Case Report

Two Cases of Pilsicainide Intoxication showing the Brugada-type Electrocardiographic Findings and Incessant Wide QRS Tachycardia

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We have experienced two patients with the Brugada-type electrocardiographic abnormalities and incessant wide QRS tachycardia (presumed ventricular tachycardia) induced by intoxication of a class IC antiarrhythmic drug pilsicainide. They were elderly men with impaired renal function. Plasma concentration of pilsicainide was elevated to a toxic level in both patients. After cessation of pilsicainide, incessant wide QRS tachycardia spontaneously subsided and intraventricular conduction delay with coved type ST segment elevation in V1 and V2 disappeared. In the elderly or patients with renal dysfunction, we should be very careful regarding dose adjustment of pilsicainide or it may be better to avoid using this drug. (J Arrhythmia 2008; 24: 219–223)

Key words: Brugada-type electrocardiogram, Incessant wide QRS tachycardia, Pilsicainide, Plasma concentration, Drug intoxication

Pilsicainide, classified as a class IC drug, has a strong sodium channel blocking effect which depresses conduction in various regions of the heart.[1] Pilsicainide can unmask or aggravate the Brugada-type electrocardiogram (ECG) in patients with latent Brugada syndrome.[2,3] We have experienced 2 patients with the Brugada-type ECG abnormalities and incessant wide QRS tachycardia, presumed ventricular tachycardia (VT), induced by intoxication of pilsicainide.

Case Presentation

Case 1: A 73-year-old man was referred to our hospital for loss of consciousness. He had suffered from hypertension and diabetes since he was 30-year-old, and he had blood dialysis regularly in a local clinic for chronic renal failure since he was 65. He had been taking flecainide (50 mg per day) for 3 years because of paroxysmal atrial fibrillation (AF). However, two months ago, another clinic gave him an additional prescription of pilsicainide 150 mg per day (50 mg t.i.d.) for recurrent AF. On May 10, 2005, he had an episode of polymorphic wide QRS tachycardia with loss of consciousness during hemodialysis. The 12-lead ECG showed a regular wide QRS rhythm of 80 beats/min without visible P waves and marked coved-type ST segment elevation in V1 and V2 (**Figure 1**, left). He was transferred to our hospital to treat his presumed Brugada syndrome. On admission, physical examination was unremarkable. Chest X-ray revealed cardiomegaly

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with a cardiothoracic ratio (CTR) of 57.5%, but no signs of lung congestion. Laboratory examination was remarkable for renal failure (BUN 40 mg/dl and serum creatine 11.4 mg/dl) with normal electrolytes (Na 139 mEq/l and K 4.2 mEq/l) and slight anemia (Hb 10.8 g/dl). Echocardiographic examination showed a mild dilatation of the left atrium and mild to moderate hypertrophy of the left ventricle (LV) with normal contraction; the ejection fraction was 70%. After admission, his ECG showed AF with improvement of wide QRS complexes and ST segment elevations; however, incessant monomorphic wide QRS tachycardia was observed (**Figure 1**, right). Because of slow tachycardia with a rate of 95 to 100 beats/min, he was asymptomatic and his systolic blood pressure was maintained at more than 100 mmHg during the wide QRS tachycardia. We suspected IC drug intoxication due to renal failure from his medical history and ECG. Although the plasma concentration of flecainide was within the normal range, that of pilsicainide was markedly elevated to 4.52 μg/ml, which was 5 times more than the therapeutic range (0.20–0.90 μg/ml). He was treated with continuous saline infusion and hemodialysis every other day. Incessant wide QRS tachycardia spontaneously subsided after 2 days, and intraventricular conduction delay and ST segment elevation in V1 and V2 disappeared as the plasma concentration of pilsicainide decreased (**Figure 2**). He was treated with digoxin and verapamil for rate control and warfarin as an anticoagulant, and discharged with persistent AF.

Case 2: A 77-year-old man was transferred to our hospital for syncope. He had a history of thoracic aortic aneurysm, which had been treated with a total replacement of the aortic arch 2 years ago. He suffered from incomplete paralysis in the lower extremities due to spinal cord infarction after the operation. He had been prescribed pilsicainide for paroxysmal AF for more than 6 months. The dose of pilsicainide was 50 mg b.i.d. initially, but increased to 100 mg b.i.d. inadvertently 2 months before the episodes of syncope. On admission, his physical examination was unremarkable. The 12-lead ECG showed no visible atrial activities and irregular QRS complexes with incomplete right bundle branch block pattern and coved-type ST segment elevation in V1 and V2 (**Figure 3**, left). Before the admission, incessant wide QRS tachycardia with a rate of about 120 beats/min was observed at the local clinic (**Figure 3**, right). However, no wide QRS tachycardia occurred after the admission, except for sporadic ventricular premature beats. Chest X-ray showed cardiomegaly with a CTR of 53.4% but no pulmonary congestion. Laboratory examination showed mild renal dysfunction (BUN 26.6 mg/dl and the serum creatinine 1.4 mg/dl) with a normal potassium level of 4.4 mEq/l and slight anemia (Hb 10.4 g/dl). Echocardiographic examination revealed normal LV systolic function with an ejection fraction of 76% and no hypertrophy or dilatation of LV. Left atrial dimension was not dilated (29 mm). We speculated that it was due to pilsicainide intoxication from his medical history and ECG findings, and examined

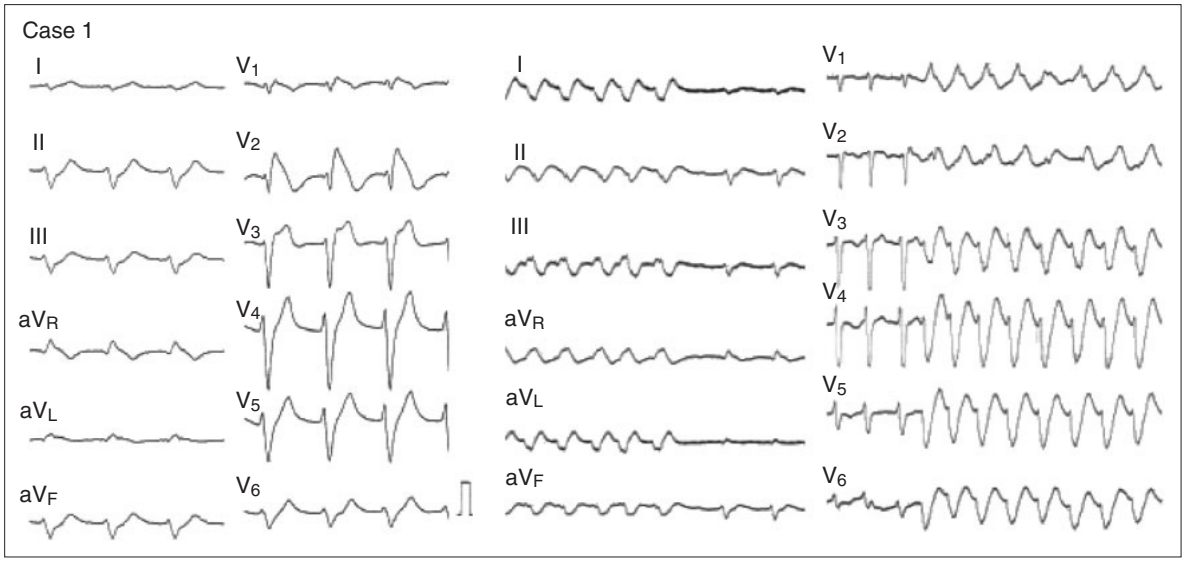

Figure 1 The ECGs in Case 1.
Left: A regular wide QRS rhythm of 80 beats/min without visible P waves and marked coved-type ST segment elevation in V1 and V2.
Right: Incessant monomorphic wide QRS tachyacardia with a rate of 95 to 100 beats/min observed after admission.

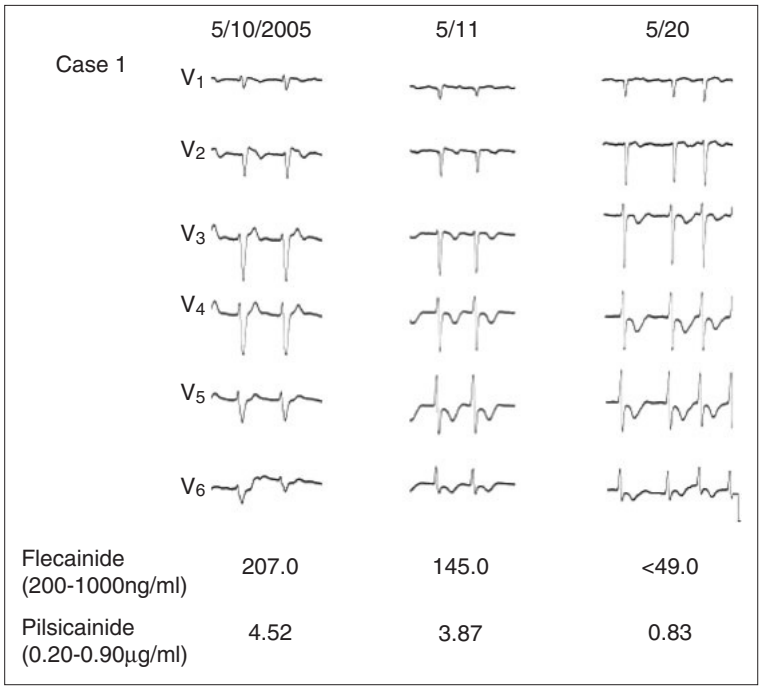

Figure 2 Association between the ECG findings and plasma concentration of pilsicainede and flecainide in Case 1.
Intraventricular conduction delay and ST segment elevation in V1 and V2 disappeared as the plasma concentration of class IC drugs decreased. The therapeutic ranges of each drug are shown in parentheses.

the concentration of serum pilsicainide, which indicated a toxic level of 4.09 μg/ml. After cessation of pilsicainide, his ECG abnormalities, including the coved-type ST elevation and intraventricular conduction delay, disappeared in association with decreased serum concentration of pilsicainide (**Figure 4**). AF was converted to sinus rhythm spontaneously and did not recur during the hospitalization. So we decided to follow up without antiarrhythmic agents, but anticoagulation therapy with warfarin was started. Then, he was transferred to another hospital for rehabilitation of lower-extremity paralysis.

Discussion

Serious overdose of pilsicainide has been reported to be characterized by severe bradycardia due to sinus arrest or atrioventricular block, marked intraventricular conduction delay, induction of VT, and the Brugada-type ECG abnormalities.[4–8] Our 2 cases are unique because a typical Brugada-type ECG and incessant wide QRS tachycardia occurred concomitantly due to pilsicainide intoxication; only one such case had been reported earlier.[7]

Pilsicainide is one of the drugs well known to induce the Brugada-type ECG findings and is commonly used for a provocation test, especially in Japan, in order to find a patient with latent Brugada syndrome.[2,3] Our 2 patients showed the Brugada-type ECG findings temporarily due to pilsicainide intoxication, and their ECG abnormalities disappeared in association with reduction of the plasma concentration of pilsicainide. Pilsicainide intoxication is not always associated with the Brugada-type ECG changes.[4–6] It is not clear that our patients have latent Brugada syndrome or mutations of SCN5A because we did not perform the genetic analysis. However, the most important issue is whether they have similar clinical characteristics or risk as those with Brugada syndrome. Priori et al[9] have reported that the patients who have a diagnostic ECG only after provocation challenge by the IC drug are at lower risk of cardiac events, and the prognosis of asymptomatic patients without a family history of SD is relatively good compared with symptomatic patients. These ST-T changes may be due to strong depression of intraventricular conduction by pilsicainide intoxication. It is not clear whether the ST-T changes due to intoxication of IC drugs are caused by a similar mechanism as Brugada syndrome. In addition, our patients only had experienced syncope after administration of pilsicainide. We made the assessment that our 2 patients have a lower risk for future cardiac events and did not perform further examinations or therapies except for withdrawal of IC drugs.

We observed a wide QRS tachycardia in each of our patients during acute phase; it disappeared spontaneously in association with reduction of the

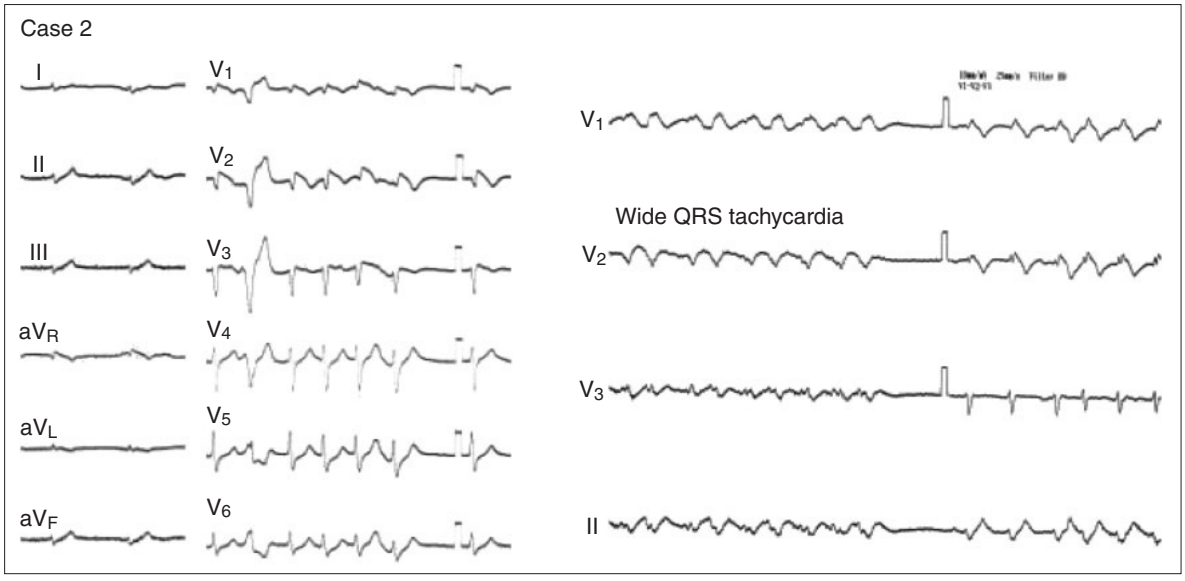

Figure 3 The ECGs in Case 2.
Left: Irregular QRS complexes with incomplete right bundle branch block pattern and coved-type ST segment elevation in V1 and V2.
Right: Incessant wide QRS tachycardia with a rate of about 120 beats/min observed in the local clinic.

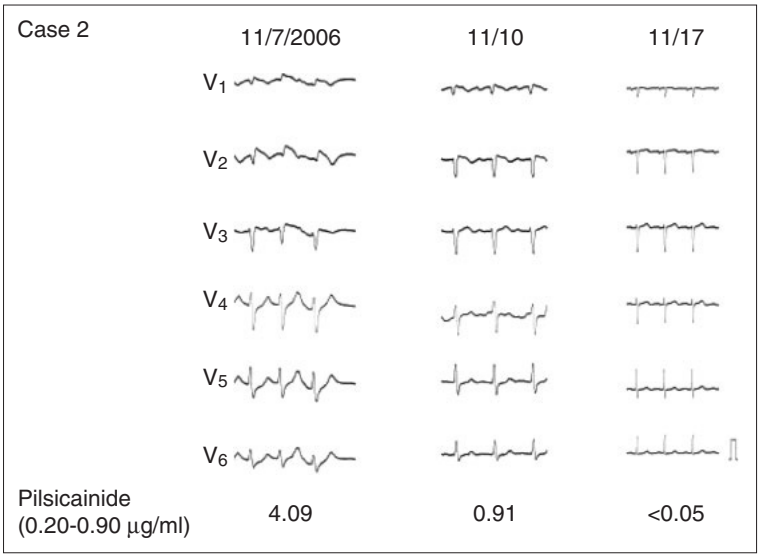

Figure 4 Association between the ECG findings and plasma concentration of pilsicainede in Case 2.
ECG abnormalities, including the coved-type ST elevation and intraventricular conduction delay, disappeared correlated with the serum concentration of pilsicainide. The therapeutic range of pilsicainide is shown in parentheses.

plasma concentration of pilsicainide. The challenge test with the administration of a class IC drug could induce lethal ventricular arrhythmias.[2,10] Incessant and monomorphic VT is well known as a proarrhythmia induced by a strong slowing effect of intraventricular conduction due to class IC antiarrhythmic agents.[11] Although we could not identify their wide QRS tachyacardia as ventricular in origin, we speculate that their incessant tachyacardia may be VT as a proarrhythmic effect due to intoxication of IC drugs.

The plasma concentration of pilsicainide was elevated to a toxic level (4 to 5 times over the upper limit of the therapeutic range) in both patients, and withdrawal of the drug eliminated the Brugada-type ECG changes and incessant wide QRS tachyacardia. Elderly patients can easily have a high concentration of the drug due to latent renal failure or decreased reserve in renal function. Although the dosage of pilsicainide was within the usual doses, 150 mg or 200 mg per day in each patient, our patients were elderly and their renal function was impaired:

regular hemodialysis administered in case 1 and serum creatinine was 1.5 mg/dl in case 2. Plisicainide is mainly excreted by the kidney[12] and the mean elimination rate by hemodialysis was 32%.[13] In addition, another IC drug flecainide was concomitantly prescribed in case 1. In order to prevent intoxication, we should be very careful regarding dose adjustment of pilsicainide in the elderly or patients with renal dysfunction, especially in patients undergoing hemodialysis, and it may be better to avoid using this drug in such patients.

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